DR. FELIX: I am sorry, there were only how many patients?

DR. JERIAN: Of the 469 patients enrolled on the study, 169 had CB11 testing done. All of the patients had -- I believe all of the patients had 45 testing.

DR. FELIX: So, that is fairly late in the enrollment.

DR. JERIAN: Yes.

DR. O'LEARY: Two things. First, I would like to ask the industry representatives to please step back from the presenter's table to make room for Dr. Jerian. And then we will -- if there are no other questions right now for Dr. Jerian after a moment or two of re-setup, we will ask for Nina Chace to -- yes, go ahead, Dr. Kemeny.

DR. KEMENY: I know these are, you know, randomized controlled studies, but isn't this a moderately low response rate for patients first treated for metastatic breast disease?

DR. JERIAN: That question came up yesterday and specifically for the Taxol(?) patients, the Taxol alone patients, and the data -- HER2 positive patients, in retrospective studies, are felt to have a poor prognosis and possibly be less responsive to chemotherapy. But that is retrospective analysis.

But other than that, I can't -- in my review of

the data and the conduct of the study, I can see no specific reason as to why those response rates may seem low in the control arms.

DR. KEMENY: And one other thing. Do you have data on how many of the patients -- are all of these patients patients who have been treated for primary breast cancer and then relapsed or are any of them who have presented in the relapse fashion?

DR. JERIAN: There are a few patients who presented with a primary and metastatic disease at the same time. The majority of -- the vast majority of patients had their primary -- at an earlier time point received therapy for their primary, whether it be surgery, radiation, adjuvant chemotherapy, subsequently developed metastatic disease. They could have received hormonal therapy for their metastatic disease, but they may not have received chemotherapy for their metastatic disease.

So, that might account for some of the difference -- partly low response rates.

DR. KEMENY: Just looking over the numbers, I mean, it seems like a funny group of patients because you have, for instance, 62 percent had mastectomy and 34 percent had adjuvant chemotherapy. It doesn't come out right for lumpectomies and radiation and --

DR. JERIAN: I tried to give an abbreviated

presentation for the purposes of this meeting, but I think what the data are saying, if you look at the baseline demographics over all in the subgroups is the Taxol patients tended to have a higher incidence of mastectomy.

If you look at the data, they have larger tumors, more nodes, positive, more reasons to have had mastectomy compared to lumpectomy than the AC patients. We looked at that data pretty thoroughly and are comfortable with it in terms of the baseline demographics.

DR. O'LEARY: Dr. Ladoulis.

DR. LADOULIS: I have a further question there, I think, related to that. What is the stratification of the patients in this AC trial by international sites versus other sites in terms of their demographics?

DR. JERIAN: They were stratified by region, the regions being North America, Australia/New Zealand.

DR. LADOULIS: With regard to mastectomy and -- are patients -- how did they stratify by --

DR. JERIAN: Mastectomy was not a stratification factor.

DR. LADOULIS: Okay.

DR. JERIAN: Whether they had prior anthracycline(?) therapy was and where their site of metastasis was, whether it was visceral soft tissue or superficial or bone only. And we looked at that thoroughly,

the site of metastatic disease and actually did an alternate analysis in that. Our definition of superficial or soft tissue disease or the standard definition that is used in the oncology community was different than what was used in the protocol in one particular element in that they called lymph nodal disease, visceral disease.

We reclassified every single patient and ran the analysis again for the distribution by using lymph node disease or soft tissue disease and, in fact, the distribution was equivalent throughout. There was good comparability in each of the arms for metastatic site.

DR. O'LEARY: Dr. Davey. And then I think we will go on.

DR. DAVEY: Okay. So, for metastatic disease it was not axillary nodes, but any other, like superclivicular(?) would be considered metastatic. Is that correct?

DR. JERIAN: Right.

DR. DAVEY: I was just curious, this recommendation about this Phase 4 commitment. If it is approved, is there -- what else is going on now? Are there NSABP(?) trials or what else would happen if this is approved that you could actually do?

I am not sure if I am being clear.

DR. JERIAN: Your question might -- well, it is

sort of for the sponsor, too. I think the sponsor is currently having discussions and has had for a long time about the development, further development of the Herceptin therapeutic program.

I think NSABP has had open discussions regarding the use of Herceptin and that has been -- I can mention that because it has been published -- that they have discussed doing studies in the adjuvant setting.

DR. O'LEARY: I think at this point it would be good to get on to Nina Chace to focus on some of the laboratory issues and there will be plenty of opportunities for more interaction.

Thank you.

MS. CHACE: My name is Nina Chace, team leader for review of the DAKO HER2 immunohistochemistry test application. I am here to present FDA questions for panel discussion. You should have received a copy of these questions.

The overhead shows the questions. So, I will just read over the questions for discussion.

The first one: Is the demonstrated concordance of the DAKO test with the LabCorp immunohistochemistry test used during the Herceptin clinical trials sufficient to justify using the DAKO test to select patients with metastatic breast cancer for treatment with Herceptin.

The second: Do the data support the claimed intended use to detect overexpression of HER2 accurately and reliably?

Given the reproducibility of the DAKO test, should the threshold for positive results be moved upwards from 2+ to 3+ to only 3+ as positive for treatment with Herceptin?

There are technical difficulties commonly associated with immunohistochemistry that were evident also during the inter-laboratory reproducibility study. Should DAKO sponsor a training program to educate and train users how to perform the test, including the proper use of the control slide to validate the assay and aid in interpretation of results? Are there additional issues that training should include?

Last: Does the panel see any additional issues or differences between the DAKO test and the LabCorp test that should be considered?

This concludes my presentation.

DR. O'LEARY: Thank you.

Now, what I would like to do before focusing on the specific questions is to ask first does anybody want clarification of any of these questions from Nina or other FDA?

[There was no response.]

Okay. If not, I would like to take a few minutes

to ask -- give the committee opportunity to ask questions that may be relevant to the overall consideration of these questions, the implications of the meeting two days ago and to just try to really focus the issues so that they come together with each other.

I would like to ask -- I would like to blind side Dr. Miller by asking if she would like to add anything about her perspectives on the committee deliberations on Wednesday?

DR. MILLER: I think there was quite a good review. But I would like to just make a statement about the 2+, the 3+, because I think that was -- I think it is very relevant to this committee. It is my opinion that the committee was different from many of the others on the committee. So, I am going to give you sort of a general -- the whole committee's, not my opinion, on that issue at this time.

There was very strong sentiment in the committee that clinicians and even looking at the data, that there is enough interest in this treatment and enough potential users of this treatment that they did not want to exclude the 2+ patients from potentially being able to use this Herceptin. Even given the response rates that they will talk about for the 2+, there was a strong feeling that the study was not designed to look at 2+ versus 3+. We are using a different

antibody or a different test and so you may truly be taking patients, who may respond and not giving them -- and denying the potential use.

So, there was a lot of discussion, but then it really did come back there. I think many people did feel more comfortable with the fact of giving the data what 2+ plus equals, what 3+ equals and then allow the physician and the patient to make a risk benefit analysis and coupled with that, the Phase 4 commitment question that came up, to go ahead and look after marketing or after approval, with the new test, if there really is no benefit to the 2+, then you wouldn't want to continue doing it, but there is enough question and there was enough feeling that there is potential clinical benefits to not say that group of patients should not be allowed this drug.

I think that was my -- so, that is how we came about this discussion. I actually was hoping that they would vote on that at the end because I think that really was a better discussion for that panel than this panel, what the cutoff should be because the cutoff of where you are going to use the test is -- how you are going to use that data is actually a clinical decision based on risk and benefit to the patient.

DR. O'LEARY: Is it your sense that the discussion that the reason for the heterogeneity of opinion was

influenced by a general perception in the panel members that immunohistochemical tests, this one included, intended to be irreproducible and hence -- and between that and the fact that this was a surrogate for the original test investigated, it was just unclear how it would fit into management?

DR. MILLER: Yes. There was general concern about saying that this should only be used in a very specific population because of the question about reproducibility of the test, variability of any test and the question that this is a surrogate marker and all the things -- I think if everybody thought that the test was definitive, that they knew that a 3+ was always a 3+ and a 2+ was always a 2+, well, then, yes, it makes sense that you may want to consider it only as a 3+, but people didn't feel comfortable enough that everybody could distinguish a 2+ from a 3+, that they didn't want to deny the 2+ who may really be 3+, the potential for using this drug.

Making such strong commitments in any package insert does impact on not just the ability to use the drug, but also reimbursement for the patients when they use this. And there may be reasons why a patient who has 2+, but has other factors or whatever, you may want to use this and if it is only -- and that was, I think, the reticence because it is not just indicating -- it does indicate on patient

impact, as well as reimbursement.

DR. O'LEARY: That was my sense and I just wanted to ask one more question to see if I have it right in terms -- and this has the influence on the laboratory performing the test as a clinician and a patient might make a risk benefit analysis. The comment was made, I believe, by one of the cardiologists that had been impaneled that this therapy was roughly -- had a cardiotoxicity comparable to that of anthracyclines. Is that correct in terms of the comment that was made?

DR. MILLER: Right. I think that sort of the comment was, yes, that the fact that they thought that it did have significant potential cardiotoxicity and we don't know whether or not we can explain all the cardiotoxicity from prior anthracycline or whether it is an independent cardiotoxicity. We just don't know enough. So, we have to accept that this drug has a significant potential for cardiotoxicity and have to use that when you are making risk benefit assessments.

DR. O'LEARY: Okay. Thank you.

Do you have anything else you wanted to add in response to that, Dr. Jerian?

DR. JERIAN: Maybe I can just clarify, Herceptin as a single agent was given to very few patients, who had not received prior anthracycline therapy. Of the patients

that I showed you, who had cardiotoxicity, who received Herceptin alone, two had not had prior anthracycline therapy, but they had preexisting cardiac disease at baseline.

We don't know if Herceptin alone, what level of cardiotoxicity it has and what severity, what incidence and severity. I believe it does by itself, but it is impossible from the data that is -- the studies conducted to date to make any conclusions about Herceptin alone in anthracycline naive patients.

DR. O'LEARY: Okay. Thank you.

Dr. Miller, did you want to say something else?

DR. MILLER: No.

DR. O'LEARY: Okay. I would like to take the opportunity then to ask a question of sort of the combined review staff and maybe of the statistical staff as well.

As I look at the original concordance between the CTA and the DAKO studies, I saw that this had been presented in the PMA using Cohen's(?) KAPA(?), which I thought was sort of an unusual way to try to measure laboratory test concordance. That is usually used for intra-observer variability, which is fundamentally a different thing.

So, I went back and reanalyzed this data doing both Pearson's(?) and Stearman(?) correlation coefficients. Stearman, you know, is a rank order correlation and Pearson

assumes basically that you are measuring exactly the same thing. And I come up with an r-squared of about .48 or .49, suggesting that about 50 percent of the variance in the assay is explained by the concordance between the two and 50 percent of the variance is due to other factors.

Am I misunderstanding in some fashion or another the degree of concordance of these two assays? I was asking particularly if we have an FDA perspective on that.

Yes.

PARTICIPANT: I am the CBER statistician. I didn't review the data but I could make a comment about Stearman's correlation and concordance.

DR. O'LEARY: Okay. Thank you.

PARTICIPANT: They are very different measures, in fact. You could have -- I wasn't prepared for this so I can't give you clear examples, but certainly the example actually that the company gave, if you remember, when they were talking about why they used a 50/50 split and they said that had they used a 90/10 split with the 90 percent being positive and they had taken a dumb test, namely, just call everyone positive, then they would get a 90 percent concordance.

If they had looked at the Spearman's rank or some correlation coefficient, they might have seen no correlation. So, there can be, in fact, zero correlation

that in other words there is no association between the tests.

DR. O'LEARY: I understand that, yes.

PARTICIPANT: So, the question is what is relevant in this case, what is a relevant measure, I mean, you could have --

DR. O'LEARY: That was basically what I was looking toward was an FDA perspective on the relative -- on the relevant measure.

PARTICIPANT: The correlation coefficient you see is conditional upon how many each test is calling positive. So, if you have both tests calling a lot of them positive or both tests calling a lot of them negative, you could -- well, let me put it this way. If both tests were calling 90 percent positive, okay, and then you would expect if they were independent tests, if your correlation --

DR. O'LEARY: You would have big problems here.

PARTICIPANT: Then you would have 90 percent times 90 percent. So, 81 percent of them both being positive with zero correlation, but you would have high concordance.

DR. O'LEARY: Right.

PARTICIPANT: And I guess the question that you have to consider is whether concordance is the relevant thing to measure when we are comparing two tests.

DR. O'LEARY: I guess my question would sort of

suggesting that it --

PARTICIPANT: And I think we decided that, yes, probably when we really wanted to see if the tests are agreeing, that concordance is probably more relevant than independence because independence is based upon conditioning upon the total number of positives and negatives.

DR. O'LEARY: Well, no. In fact, what we were suggesting, though, is that the two go together, the two tests that are perfectly concordant will -- obviously, are not independent and the issue for me was how does one look at this issue of how good the concordance is. And the problem with the interpretation of Cohen in this circumstance is that, first of all, it is -- while it corrects for the probability of trans-association, there is not really a rigorous understanding of the meaning of the number itself. That is an interpretation issue.

PARTICIPANT: That is certainly true. On the other hand -- well --

DR. O'LEARY: That was just a question from me. And I know you are going to want to address this and we will give you an opportunity later. I wanted to give a chance to get the FDA staff on this.

Yes. Does Dr. Campbell want to comment? Dr. Campbell does not want to comment. Okay. That is fine.

Yes, Steve.

DR. GUTMAN: I would like to just make a comment before you go further into the discussion and that is in terms of blindsiding, we actually blindsided our lead reviewer, Nina. These questions are on the table and I would like to suggest that we have a lot of background information that we, as well as the company, would be willing to prepare or present or you walk through these questions.

We actually did have a formal presentation to outline the FDA perspective, but thought that the relevant information had been very reasonably summarized by the company and that the background had been very nicely dealt with by Biologics. For the sake of trying to allow the proceedings to move along, we truncated, actually we eliminated the formal presentation. It is still there and we have lots of information we would be willing to share if there are any nuances or issues that come up as you walk through these questions.

These questions are the essence of what we have identified. They don't exclude you from identifying other tough questions either from your analysis of the data or from your interaction with the committee on Wednesday or from those of you who didn't interact, your understanding of the interactions from the committee on Wednesday.

And the essence of the statistical question you

raise, there actually are two issues. One is the issue of how it affects the way you might answer Question No. 1 and the second issue is assuming that you answer Question No. 1 in the affirmative, that you still are comfortable, whether you want other statistical treatments to be added to our analysis and/or whether you want any labeling caveats to reflect any of the concerns you might have. So, you have a lot of options.

PARTICIPANT: I just want to say one thing. Although they reported Cohen's KAPA, it was -- the test was actually based upon concordance, which was the --

DR. O'LEARY: No, I understand they are raw numbers basically.

PARTICIPANT: So, they are looking at a binomial proportion and taking it under --

DR. O'LEARY: I understand that.

PARTICIPANT: Oh, okay.

DR. O'LEARY: I guess at this point -- yes, Diane.

DR. DAVEY: I had just a couple of questions. I was looking quickly through the FDA handout. There is a page on the LabCorp -- it is inter-laboratory reproducibility studies and then LabCorp versus original score in pilot study. I am not sure that I am understanding exactly when those two tests were done.

And the other question was the very last thing I

got in the mail about whether I think LabCorp had -- I think there was a tendency to call things higher. The information that I got back, I didn't quite understand exactly how many of the things had changed and what difference that had made to the results.

So, if I could get some explanation, that would be helpful.

MS. CHACE: What this represents is the inter-laboratory reproducibility study and to do this study, the sponsor chose samples that were in the original pilot study. They took 40 samples out of the original 103 samples, I think, and they chose them such that -- as you can see over here on the right hand column, they chose them to have equal numbers of the 3, 2 and 1+.

DR. DAVEY: Okay. The studies were run at different times, the same block of tissue, but they are run at a considerably different time. I mean, the block was recut and then run again with the --

MS. CHACE: Right. And the original study in July of 1997 and the reprodicibility study, I think, was like March of 1998. They recut from the blocks. So, we had the company go back and reexamine these samples, the reproducibility samples and the original LabCorp study samples and, indeed, there was a difference in intensity. So, it wasn't the reading of the slides, but the slides were

more intense when -- during the inter-laboratory reproducibility study. And the only thing that we could come up with, the difference was that they used the Tech-Mate -- they used another automated stainer to do the pilot study and they used the DAKO autostainer to do the reproducibility studies.

So, the only difference that we could really lay a finger on was that a different autostainer was used.

DR. DAVEY: But the manual was done exactly the same way and the antibodies and everything else were the same.

MS. CHACE: The LabCorp -- the pilot study was all automated.

DR. DAVEY: Okay.

MS. CHACE: In the reproducibility study, they did it two different ways.

DR. DAVEY: What did you conclude from that information that was just sent out to us in terms of when the slides were sent out again for review?

DR. FELIX: The justification, I think --

DR. DAVEY: There has been minimal -- like, for example, in this thing sent out in August, I wasn't quite sure what the new reading of the slides in Appendix 1, and there have been minimal differences in staining intensity interpretation between pathologists. I didn't know what

that minimal -- I wasn't quite sure what to make of that minimal. I mean, was that something that was a concern of yours, the difference between pathologists' reading or did you think it was more the staining run?

MS. CHACE: Well, we didn't know whether it was the subjective differences between different pathologists reading or whether it was actually a difference in staining of the slide. It looks like it was a difference in the staining of the slides and the only difference was that two different autostainers were used.

DR. DAVEY: Okay. So, the minimal really is minimal then? Sometimes I just wasn't sure if the minimal readings between pathologists, that is -- you agree with that, that there is really not very much difference.

MS. CHACE: Well, the expert pathologist, who reread the slides actually got more positives than the LabCorp got.

DR. DAVEY: Okay. Would that make a difference in the overall results of anything else, that difference in reading of the slides?

MS. CHACE: Well, I think it just shows that there is variability. I think this shows that probably we need to, if we want to get consistent results, maybe limit it to the DAKO autostainer possibly. Different autostainers can give different staining results.

I may not be absolutely sure about this, but I think the clinical trial assay was run on this other autostainer. So, the clinical trial assay may -- if the autostainer is staining more weekly, the clinical trial assay may also be getting fewer 3+ and 2+ results.

DR. O'LEARY: Dr. Ladoulis.

I think that looking at all the sources of variability in this type of assay, there is the biological variability that we know and I think I will come back to that in just a minute.

The second is the variability introduced by the handling, whether it is the fixation from one laboratory to another or the time and the temperature at which the specimens and blocks are kept and slides are kept and also the variability and the handling by the laboratories in the conduct of the immunohistochemical assays, which has already been referred to.

Finally is the variability of the observer variation. So, given those sources of variability, I think to err on the side of safety, it would be better to concur that the concordance exists, at least for those samples that have the high score of 3+ by the DAKO analysis. I think I would feel very confident about those in respect to an assay that would warrant a clinician to provide an option for Herceptin therapy.

As far as the other scores of 1 and 2+, one of the other concerns I had was in the document, the threshold level is for 10 percent or more cells being positive as one of the thresholds. However, when you look at down to sites in which the raw data is recorded, at the various sites in which they have actually performed the immunohistochemistry, those specimens that have 3+ or even 2+, they are atypically 80 to 95 percent of the tumor cells are positive.

So, the threshold level that is adopted by the sponsor in the application of 10 percent or more of the cells being positive is very low and I think is probably too low and I think in most laboratories that conduct these kind of tests, the scoring is actually -- it takes into account not only the intensity of the scoring but the number of cells that are positive.

Therefore, if there is going to be some change in modification and labeling and instructions done, I think it ought to be that positives ought to be considered those with 3+ and the numbers of cells that are positive ought to be greater than 50 percent at least.

DR. FELIX: I know that it is very interesting and actually necessary to talk about the variability of immunohistochemistries using it as a determinant for something, but I keep coming back into my own mind that, in fact, the clinical trial for Herceptin was run with that

assay. In other words, it was entirely dependent on the amino histochemical results of the assay.

DR. O'LEARY: A different assay though.

DR. FELIX: A different assay. And that different assay showed a response in the 3+. Now, from the presentation -- I was not at a meeting a few days ago -- it looked at virtually all -- only the 3+s were responding significantly, which concurs with your --

DR. LADOULIS: Yes. Mine were 2+.

DR. FELIX: Right. Virtually nothing to the 2+, but I think that they used a 10 percent threshold during that study. Then the 10 percent threshold is a valid threshold because that was the guidelines that they utilized in the study. And to alter that would potentially put into jeopardy the significance of the clinical study that was run.

So, I don't have a very big problem with the 10 percent threshold. It is probably never an issue. The ones that are 3+, a lot more than 10 percent of the cells are positive.

Now, the question that I had together with Dr. Davey that I think is probably answered by the supplement. And I think I was pretty satisfied with how many patients did the variability change from positive to not positive and the numbers were -- I think only one of them went from a

score of 1 to 3 and anybody else just stayed at one variable.

Is that your interpretation also? It was difficult to interpret this table.

DR. DAVEY: Yes. The columns, I think, were a little confusing. What exactly was meant by the different -- which result was which.

MS. CHACE: I broke out the three valid inter-laboratory reproducibility comparisons here. LabCorp with the reference method, so put it on the top. And these two are Site 6. This is Site 6 manually and Site 6 automated and LabCorp, this is compared to Site 2, Site 2 automated. Site 2 manual was invalid. So, this is all the three sites, LabCorp, Site 6 and Site 2.

The double lines indicate a cutoff of 1+, 2+. Here is the DAKO score. I put the positive at the top and the negative at the bottom because I am more used to that. So, these tables are reversed from most of the ones you have seen today.

Okay. For a 1+, 2+ cutoff, these are the concordant results and these are the discordants and these are the 1+, 2+ discordants. So, there are three 1+, 2+ discordants here, seven here and one here. Discordants that are not 1+, 2+ are one and two. So, you can see there are many more 1+, 2+ discordants in the inter-laboratory

reproducibility study.

Now, if you change the cutoff and move it up to 2+ versus 3+, then the gray squares become the discordant results and the white squares are the concordant results and if you add up the number of discordant results and compare them to the 1+, 2+ cutoff, in the inter-laboratory reproducibility study, there really isn't much difference. There are 15 discordant results for the 1+, 2+ cutoff and 13 for the 2+, 3+ cutoffs. So, in the inter-laboratory reproducibility study, moving the cutoff doesn't help much, but it does help a lot if you look at the concordance study.

Do you want me to show a slide on the concordance study?

PARTICIPANT: I would like that.

DR. O'LEARY: Okay. Please.

MS. CHACE: Okay. This is the same type of diagram for the concordance study. The double lines indicate a 1+, 2+ cutoff and the gray shadings a 2+, 3+ cutoff and so for this, the 1+, 2+ has a concordance of 79 percent, the 2+, 3+ at 88 percent. So, it does improve -- you get many fewer discordant results when you move the cutoff up to 2+, 3+ in this -- in the concordance study.

DR. O'LEARY: That is beautiful.

Dr. Miller.

DR. MILLER: I think we are looking at two

different things. We are looking at concordance between the inter-tests and then the other question that keeps coming back is what about 3+ versus 2+. I know you need to have negative tests -- and I am getting back to my question before about the samples that were actually on the patients who were on the trial.

The patients who are 2+, 3+ with the LabCorp clinical trial assay were actually entered on the trial consent form.

To get to the second question that people keep asking is what does having a 2+ with this test mean. You can actually get that data from just the 2+ and 3+, the patients who were on the trial. Correct? Because you can say -- right? You can get that data if you had those specimens. Correct?

DR. COHEN: Is your suggestion, Dr. Miller, to go to the patients enrolled on the trial?

DR. MILLER: Yes. I think you can use a commercial data bank to get the concordance between two tests and I think you have done that. I think you have done that question.

The next question is for the clinicians and how to make the 2+ versus 3+ cutoff. And for that it doesn't matter if you have zeros. We don't care about zeros. What we care about is the patients who were on the study. You

have got a wealth of patients on the study. Why not try and figure out for this test whether or not a 2+ means anything and get that data.

I think it would help us a lot. I don't think it necessarily needs to be done beforehand. I think it could be another postmarketing commitment because people want to be able to figure out how to use this. I think, especially given the fact that we do know that there is toxicity with the drug, albeit anything there is a risk benefit ratio, I would really like to know that information when I am using it in patients. That we can get because you did get informed consent on those patients and you should be able to go back and get the blocks.

DR. O'LEARY: Would the sponsor like to comment on this? We will come back to this question. Then I am going to go to focus going through the questions and we will come back and address this in some detail.

DR. HELLMAN: My name is Sue Hellman. I am chief medical office at Genentech.

With regards to the question of what Dr. Miller is bringing up, I am very sympathetic to what you are asking us to do. I think we would like to go back and retest those patients. We talked a lot about informed consent. And one thing I would like to raise, we did this study in multiple countries. So, we are all applying U.S. rules. There were

patients in Australia, New Zealand, in multiple countries in Europe, as well as the U.S.

So, what I am concerned about listening is that we commit to a Phase 4 commitment that is undoable. I would hate to see that. I do think we are very much able going forward to do as you ask in a Phase 4 commitment.

Let me raise one study in particular to give you an example of the types of trials we are carrying out. One of the planned studies in metastatic breast cancer is a trial in 200 patients with metastatic breast cancer very similar to the patient population in our pivotal Phase 3 study.

The trial will be done using Taxol and carboplatin(?) plus or minus Herceptin. All patients in this trial with have both DAKO testing and FISH(?) testing and we will have the ability to look at 2+ and outcome, as well as the ability to look at 2+ as compared to FISH testing. That type of Phase 4 commitment is one that we are very much willing to commit to.

I am concerned about trying to go back as we did for this study because I don't think we can get there with a multiple country, multiple hospitals, multiple consent form issue.

DR. O'LEARY: We will come back to this threshold cutoff a little bit later in the discussion. I think it is

very important.

I would like, in the interest of time and moving through things, to try to address the FDA questions directly and in order. Okay. Since we are moving into the panel discussion phase at this point, we would like to ask the FDA reps to excuse themselves from the table, although we will feel free to call on you if we think that clarification will be helpful.

Agenda Item: Open Committee Discussion

So, I would like to start with the first question asked: Is the demonstrated concordance of the DAKO test with the LabCorp IHC test during the Herceptin clinical trials sufficient to justify using the DAKO test to select patients with metastatic breast cancer for treatment with Herceptin?

I would like to just ask each panel member in order. I am going to go around the table to give their answer. If they want to pass on the question, that is fine, too, and then we will have a second opportunity to respond or go into detail.

Dr. Ladoulis.

DR. LADOULIS: In answer to your question, yes, I think there is sufficient evidence to justify using the DAKO test to select patients for treatment with Herceptin, with the qualification of the scoring to be addressed later as to

the threshold level.

DR. O'LEARY: Dr. Davey.

DR. DAVEY: Yes, I agree completely with Dr. Ladoulis. I would like -- I would answer "yes," but I think we need to come back to where we cut it off and labeling.

DR. HORTIN: I would say "yes," with the qualification that they have shown concordance at one laboratory, LabCorp, they can get concordance. I think that they basically have some issues in terms of labeling and some of the scoring and interpretation issues, but I think they have showed that it is possible to have some concordance, but they haven't shown that in kind of general practice, it is probable that it will happen.

DR. O'LEARY: So, we will come back to this in .4, as well.

Dr. Miller.

DR. O'LEARY: Oh, Dr. Felix. I am sorry.

DR. FELIX: It is my size. It happens.

I agree with the other panel members. I think that they have demonstrated it.

DR. O'LEARY: Dr. Miller.

DR. MILLER: I vote "yes."

DR. O'LEARY: Dr. Floyd.

These are comments not a vote.

DR. FLOYD: I think this has been very good.

DR. O'LEARY: Ms. Rosenthal.

MS. ROSENTHAL: Yes. I do think they showed concordance between the two assays.

DR. O'LEARY: Dr. Kemeny.

DR. KEMENY: I agree. I think they showed concordance.

DR. O'LEARY: As do I.

Then we will move on to the second -- does anybody want to amplify on their comments anymore at this point? Okay.

Second question was: Do the data support the claimed intended use to detect overexpression of HER2 accurately and reliably?

Again, Dr. Ladoulis.

DR. LADOULIS: Yes, I think the data support the detection of overexpression with qualification as to inter-observer variability and inter-laboratory variability.

DR. O'LEARY: Dr. Davey.

DR. DAVEY: Again, yes. We have to get back to the reproducibility later.

DR. O'LEARY: Dr. Hortin.

DR. HORTIN: Yes.

DR. O'LEARY: Dr. Felix.

DR. FELIX: I will pass.

DR. O'LEARY: Dr. Miller.

DR. MILLER: Yes. I feel they show that they can detect overexpression of HER2 accurately and reliably.

DR. O'LEARY: Okay. Dr. Floyd.

DR. FLOYD: Yes.

DR. O'LEARY: Ms. Rosenthal.

MS. ROSENTHAL: Yes, I do. I think that this has demonstrated great specificity, but in the real truth or in Dr. Press's -- compared with Dr. Press's results, I am not sure how sensitive it is.

DR. O'LEARY: Okay. Thank you.

Dr. Kemeny.

DR. KEMENY: Yes. I think it supports this.

DR. O'LEARY: I think that is true as well.

Now, I guess before getting comments on Point 3 and, again, being aware of the time that we are supposed to be breaking in roughly ten minutes, I would like to have a little bit more open discussion related to Point 3. The question of given the reproducibility of the DAKO test should the threshold for positive results be moved from 2+ to 3+. So, we will go back to sort of the show of hands of back and forth questioning on this before going around round robin sort of comments from the panel.

Dr. Ladoulis, you made -- or Dr. Davey.

DR. DAVEY: I think what the FDA staff was getting at and what I am bothered about, too, is now seeing these

pictures, is I am having real problems with the 1+ versus 2+ in the pictures. And I think the 3+ is more clearcut. On the other hand, that clinicians are going to want to know what some of the 2+ ones, but my problem is not so sure telling what -- it is the distinguishing between the 1+ and 2+. I think perhaps we are going to have problems.

I also have problems with reporting to the clinicians 1+, 2+ and 3+ because I think a lot of clinicians are not going to completely read the package inserts and they are going to think 1+ is positive. So, they are going to -- you know, any positive result -- and I understand you can't just call it negative because when you have your controls, that one control has to read somewhat positive and it has to be a 1+ control. So, that is a problem I see.

But I think the 1+ versus 2+ is really hard to see in the pictures.

DR. O'LEARY: Maybe I can address this question to members of the panel and if anybody from FDA or DAKO wants to step up -- what if we were to redo this and the issue would be negative, positive and indeterminate, what would that do in the way of the usability and the interpretation of the data? I mean, then we still have the question of what goes into the indeterminate category.

We have got, you know, clearly 3+ is positive. We all agree that 0 and 1+ for purposes are pretty clearly

negative. Maybe 2+ should be indeterminate, given the status. Open question. Any reactions?

Dr. Ladoulis.

DR. LADOULIS: Yes. I think that is a good suggestion. I think the reason that I am concerned about this reproducibility is that the intent of the test is to stratify patients for treatment, which is going to be a significant benefit if it is 3+. That is known.

From the clinical trial data that was submitted from LabCorp, when we have the data of the outcomes, the 2+ clearly do not have any benefit in terms of survival nor in time to progression. Whereas, for 3+ positive, they are.

To the extent that we don't know the absolute concordance in the future with outcomes with DAKO and with outcomes clinically, until you do some more prospective studies, we can be confident about a position of 3+ is really probably going to have the same outcome as a 3+ done previously by LabCorp on a clinical test assay. But it would be indeterminate with a 2+ or a 1+.

DR. O'LEARY: Dr. Kemeny.

DR. KEMENY: I don't think that would be a good idea. I think, you know, putting an indeterminate in there is just going to confuse the issue. I think often at these panel discussions, we are trying to look into the future to something -- we don't really know what the future is. We

don't really know what the use of Herceptin is at the moment.

I mean, we have some ideas that it is useful for 3+, but we don't really know where 1+, 0 or 2+, you know, fit into the scene in the future and we are only going to know that in the future.

I think, Charles, I didn't agree with your original comment about the 1+ people. I think we should get as much information as possible in the future. We want to know where the 0's, 1+, 2+ and 3+ fit in. You know, the patients will want to know and we want to know.

And it is not clear at this time and I think we should just, you know, leave the panel as it is, putting people into each category, understanding that it is imperfect because it is one person looking at a slide and then saying, well, this looks like 1+, you know. And that being true in all of these immunological tests, I would leave it personally as it is and then see what the future has to bring as to where Herceptin is useful and the other drugs and other things that might be useful.

DR. LADOULIS: I have no quarrel with keeping the scoring in place or -- rather than changing the actual stipulation of what the scoring of the test is. My concern is when labeling -- and when claims are made and it may not be claims by the sponsor now, it may be claims that are made

by others, who may use the product in the future.

The tendency I think we have seen in the past with other similar analogous types of products is that there are over-claims made to clinicians, specialists. You know, the urologists and the urology community are up in arms about some things now that we have approved before.

I think that is the concern I have is that the claims may be greater than what was intended when this was introduced. I think if we can reserve the judgment about what the values of 1+ and 2+ are pending future research, that is okay.

The question is what is it that is justified to lead to an approval for a safe and effective device now that can be marketed to the public essentially.

DR. O'LEARY: Dr. Floyd, first.

DR. FLOYD: I would like to make an observation here. We are looking at this scoring system as though it is linear. In point of fact, if you go back and look at the way the assay was set up, it is based upon expression of molecules that is logarithmic.

The other issue we are dealing with here is we are looking at a human observing things with an eyeball, whose response also happens to be logarithmic. In point of fact, we don't know where that cutoff is. The other thing we know -- and it is well documented in the literature. There are

many published studies on this -- that a score, reading scores of densities of objects, that a microscope will vary the score depending upon a variety of factors, that they just come in from lunch and were out in the bright sunlight. What is the ambient lighting in the room? There are dozens of other factors involved.

The point is that we are trying to put a linear score against a logarithmic standard here and, in fact, we also know that most of us on a good day can see maybe 30 -- the literature says up to 50 or 60 gray levels. A simple little old camera can pick out 256 gray levels and a 12 bit camera gets over 4,000.

We don't have that kind of data here. We are dealing with the real world of human beings who are doing their best to give an accurate assessment of a logarithmic point. But I would caution us against setting up artificial criteria and saying we are only going to look at the absolute maximum responsiveness, that is, in terms of overexpression, for treatment and restricted from others because otherwise we will never know where that line really needs to be drawn.

DR. O'LEARY: Dr. Felix.

DR. FELIX: Again, I agree with leaving -- with the concept of giving the data. The data is, as you mentioned before, we all need it desperately to determine

the closest approximation to truth. Nevertheless, I reiterate that despite all of these parameters that you have outlined, the initial study that has so clearly in my opinion shown that there is a difference a 2+ and a 3+ was determined by these pathologists with their mediocre eyes on or off coffee and that the data is extraordinary.

In other words, right now the only data that exists really shows a very significant difference between 2+ and 3+. I think in this -- although the antibody that we are talking about today or the assay that we are talking about is different, it is a very similar assay and a very similar end product.

So, I think that there is a consideration to be made. Of course, I am not sure it is our responsibility to make a recommendation of what is positive or negative -- excuse me -- I think it is our obligation to say what is probably positive or negative and it is then up to the clinicians whether they want to give drug to a borderline negative and then follow this patient up in the future.

But it will probably will be an experimental procedure, an experimental protocol.

DR. O'LEARY: Dr. Hortin.

DR. HORTIN: I tend to think that Dr. O'Leary's suggestion was really kind of right on target in terms of practical application. And I do favor the availability of

the data for, say, a Phase 4 study for kind of internal consumption. And you may at some point derive a deeper understanding of what these things mean, but there are so many examples when we provide results, that we either establish a normal range, say, for an iron level or for a cutoff level for an abused drug or a urine dip stick and we call something a 1+ and it so often results in somebody doing an extensive therapeutic workup or starting treatment simply -- it may be a normal variation, but so often whenever you have something that has a positive sign there, even when you say that that is not appropriate for treatment, it is misinterpreted and so many people go and look at the fine print of the package insert, that it is much more to the point, I think, to give a negative, intermediate and positive designation.

I think it addresses Dr. Ladoulis's concern about kind of the one process that really there is no data to indicate that there is any value in pursuing a specific treatment with those and I think we are looking at kind of two situations here; one, the value in terms of a research setting where it is oftentimes of greater value to stratify greater and you may find value in terms of that stratification, but I think in terms of the current understanding and practical application that really kind of the negative, intermediate and positive, that suggestion by

some similar classification is really on target.

DR. O'LEARY: We will come back to that this afternoon. I am sorry, Diane, but Dr. Hortin is going to get the final word for this morning. But at 1 o'clock, you are up next.

So, we will reconvene at 1 o'clock and I will start yelling at people at five minutes of to get in here.

Lunch, for those that ordered lunch, will be out there someplace.

[Whereupon, at 12:18 p.m., the meeting was recessed, to reconvene at 1:00 p.m., the same afternoon, Friday, September 4, 1998.]

A F T E R N O O N S E S S I O N [1:02 p.m.]

DR. O'LEARY: Okay. We are going to reconvene this meeting of the Hematology and Pathology Panel.

Dr. Diane Davey had had her hand up at the end of the last session and so she begins.

DR. DAVEY: Okay. We were talking about changing the reporting in some way to like a negative and maybe borderline and positive. While I --

PARTICIPANT: Indeterminate.

DR. DAVEY: Indeterminate. All right.

In theory, that might have some advantages. The problem I have is going back to the DAKO company and that control line, which had to have a little bit of staining in order to say the run was valid. So, for reporting that might be good, but then I would worry if we called the 1+ negative, the labs would ignoring that. So, you have to have some way of making sure that the controls in the run were run correctly.

I would also like to -- it would be nice if there was some sort of 2+ control. I mean, the main concern I have is two things, is making sure that that 1+ is evaluated correctly by the laboratory in terms of the control cell lines so that they can tell the run is valid. The second thing is how labs tell 1+ from 2+. So, I don't know if we need to have another control.

I don't think that the pictures here are quite what I -- you know, I think there needs to be a bigger range of pictures and everything for laboratories to use.

DR. O'LEARY: Okay. Thank you.

One of the things that strikes me is I am used to thinking about immunohistochemistry from the most part is a -- I have demonstrated the antigen. I haven't demonstrated the antigen. And a failure to demonstrate the antigen doesn't mean that it is not there.

I know that there were several -- that the sponsor wanted to make a comment and I wanted to know whether any of the FDA review staff wanted to make a comment about this issue before I go around the table again and sort of try to solidify at least a set of individual comments with regards to this question of threshold and reproducibility.

Did the sponsor --

DR. COHEN: Thank you for giving me the opportunity. The nature of my comment was simply to introduce someone who is a clinician, who we have worked with. And I think what is missing to some extent from your discussion, and I am mindful of what Dr. Miller said at the outset about how ODAC viewed 2+ patients.

I just wanted to ask Dr. Sandy Swain(?), who is a practicing oncologist, formerly at Georgetown and NCI, to make some comments about her view as she takes in this data

with regard 2+ and 3+ patients.

DR. O'LEARY: Thank you. I just would like to ask you to identify any financial interests or so forth as you come forth, or lack thereof.

DR. SWAIN: Yes. I am a consultant for Genentech for this meeting and for the ODAC Advisory Committee meeting.

DR. O'LEARY: Thank you.

DR. SWAIN: As Dr. Cohen said, I am Dr. Sandra Swain and I wanted to speak to you for a couple of reasons; one, as a patient advocate because we haven't heard any patient advocates here today.

I spent four years on the ODAC Advisory Committee myself and just came off in June. And frequently we had patients come and I think that perspective was very helpful.

Just from listening to the discussion, I know you are struggling with this and I know how difficult it is, but I can tell you as a physician dealing with patients everyday, it would be very difficult, as Dr. Kemeny mentioned, to tell them that they are indeterminate when you really do have a result, either a 2+ or a 1+.

I think that comparative to really give the information to patients -- and breast cancer patients especially are consumers, they want to know this. From my point of view, it is important that they have that

information, the physician has the information and they can make the decision.

The other aspect of it is as you all may or may not be aware, the majority of breast cancer patients who have metastatic disease are dead in two years. So, it is a very bad thing to have and especially if they are HER2/neu positive, as you saw today and Dr. Goldstein mentioned in her presentation from the FDA, these are very poor prognosis patients.

So, to put on my other hat as a clinician/scientist, having done a lot of clinical research, when looking at the clinical trial results, which you saw today, as a whole, they showed a tremendous benefit, clinical benefit to patient in time to progression and one year survival. So, we are all, I think, convinced of that.

The problem I have with doing the subset is the subset in 2+ was very small. It was only 25 of patients. The study was not designed to specifically look at that point. If you did -- remember Dr. Cohen's slide, where he showed you, and also the FDA did show you the results for the 2+ patients, there was an increased response rate and there was an increased time to progression. It was not significant, but it was very small numbers of patients. So there is a suggestion of benefit in the 2+ group.

Clearly, as I said, these are very poor prognosis

patients. There really are very little alternatives and for me the other aspect is this is not empiric therapy. We have treated patients for years. I have sat on the committee for years looking at therapy, CPT lab and et cetera, just for one example. We don't know exactly how a lot of those work.

They work on DNA, not specific things. With Herceptin, we have a specific target. And I think even if it is 2+ and we are unsure totally in every case that it is 2+, I think we know in some patients it will benefit. So, I would make a plea to look at it scientifically and not break up the study, but actually look at it as a whole -- the patients on this study were 2 and 3+ -- and not to be retrospective in your analysis of that.

DR. FELIX: Can I add a question about your comment?

If this panel makes a recommendation, that doesn't preclude continuation of including patients in studies that are not 3+. In other words, if -- correct me if I am wrong, Dr. O'Leary, but if this panel recommends that there is a threshold of 3 for FDA approval, that doesn't preclude that under the guise of an IRB-approved protocol, you couldn't include 2+ patients and use the drug.

This wouldn't be a -- what we are struggling with a decision is once you give an FDA approval to something, then patients can receive this drug and don't have to be

necessarily followed or monitored. Once an FDA-approved test and an FDA-approved drug are out there, physicians can put patients on drug and they don't have to follow them. This is an FDA-approved protocol and what our hesitation and our tentative nature here is that if we do want to put those patients on who are 2+ positive, we want to make sure we get data on those patients, so we do eventually know the efficacy of the therapy.

My worry is that if we grant approval for use as a 2+ and 3+ that that won't occur.

DR. SWAIN: I don't want to really speak for the sponsor, but I know that they said earlier that they do plan to do and are doing a study in 2+ and actually 0 and 1+ patients also. So, that is definitely going to be done.

I just hate to see patients -- you have young patients, who are HER2/neu position, ER negative. They may go transplant. I personally think transplant is not helpful for metastatic breast cancer. Yet, we have this option in which even though the toxicity is there with Taxol, it is really not significant compared to, let's say, transplant or high dose therapy. So, I would like to see it available for this.

DR. O'LEARY: I would like to have Dr. Gutman, please, address several of these issues you have just raised, Dr. Felix.

DR. GUTMAN: If you feel strongly, you can actually request as a part of your approval that postmarket studies be done as well and if you do that and if Biologics does that, we will attempt to coordinate our postmarket requirements. So, if you are concerned about that, one way of dealing with that concern is through a request for postmarket surveillance of the study.

DR. O'LEARY: Okay. Thank you very --

DR. DAVEY: I wanted to clarify. You said you wanted -- would you tell patients if they were 1+ and what would you do --

DR. SWAIN: Yes.

DR. DAVEY: -- because, see, my concern is the clinicians want to start putting 1+ on, even though I know, you know, I realize that the oncologists that use this would, you know, be well informed of this. But then also, I think, that the labs -- there would be a tendency on the labs' part to start reporting -- the 1+, 2+ blur is what concerns me. So, I don't have a problem with putting a 2+ if we knew what 2+ was. What I am concerned about is figuring out -- is we are going to get too many 1+ patients on the drug.

DR. SWAIN: I think that, you know, I personally wouldn't treat those patients because I am very data driven. We have no data on those patients at all. So, I think that

is really up to an informed consent and it has to be in the package insert that it is only the 2+ and 3+ on which there is data.

DR. O'LEARY: Dr. Miller.

DR. MILLER: I am concerned about going to an indeterminate in that I think you are going to get the exact opposite. You are going to get people to push to say, okay, it is positive and then we are never going to really know what the 2+ means. I mean, the study was designed to look at 1+, 2+, 3+. There is data on that. I think that you put the data out there. You teach people how to look at 1+, 2+, but you don't say something is indeterminate when there is really data to say that within that constraint, that is too far.

We also not asking this committee to approve or disapprove the drug for a 2+ or 3+. We are asking people on this committee to say whether the test is acceptable and then the -- it was clearly stated in the ODAC committee that they didn't want -- you know, the ODAC committee even didn't want to make a prediction, whether 2+ or 3+ should be treated. That should be left to the risk and benefits.

So, I think should concentrate on what we feel can be called and I am just concerned that indeterminate will mean you push those people to say, okay, well, you see something there that is positive and you will never get --

you won't be able to make that 2+, 3+ risk benefit ratio.

DR. O'LEARY: Perhaps I can ask a ask a question because I am seeing, I think, certain things that are dropping down by professional subdiscipline coming out. So, one question I would like to ask -- and then come to Dr. Davey -- how many of us sitting at this table currently interpret immunohistochemical assays on a regular basis, so, we know who we are hearing from that interprets immunohistochemistry and who does not, as we talk about the meaning of these tests and how they are actually interpreted?

Thank you. That is to help clarify --

DR. KEMENY: Then you might ask how many people work with clinical patients.

DR. O'LEARY: And then the folks that work with the clinical patients; obviously, Dr. Miller and Dr. Kemeny.

So, with that, Dr. Davey.

DR. DAVEY: Okay. Maybe I can ask the -- if this is appropriate -- can I ask somebody from the company or user to tell me from these pictures, which I can't tell, how we tell -- how they suggest telling 1+ and 2+ apart, given that there are no controls for 2+? Because maybe that would help me make that -- I am going to have to know that before I make a decision on the 2+ -- the cutoff.

DR. ROEPKE: We actually stated -- and I stated

that when I went through the pictures of the staining. The written description in the insert says that the 1+ control is a faint, barely perceptible membrane staining in part of the membrane; whereas, the 2+ and 3+ controls shows complete membrane staining.

I think it is important that we focus on the fact that 2+ and 3+ cases are stained in the periphery of the cell membrane; whereas, the 1+ cases, only as a part membrane staining. If you look at these cell line pictures, you will notice we might even have a kind of -- what you could argue, a strong staining, but only in part of the membrane, as opposed to the 3+ control that is roundly rimmed all over the membrane.

DR. FELIX: I think what confused us were actually the tissue photographs that you have here that don't show that separation --

[Multiple discussions.]

DR. DAVEY: And the nuclear counterstain looks different. It makes it very -- you know, if it is a whole slide if it is -- I don't think these pictures are very good of the -- the 3+ is very nice, but I am not sure that I could reproduce -- simply tell these two pictures apart of the actual -- it is partly because the rest of this slide is not stained the same way.

DR. O'LEARY: Perhaps this will seem like -- do

you folks actually ever report out anything with a numerical value or do you generally report out your immunohistochemistry as positive or negative?

DR. DAVEY: Mostly just positive and negative. Rarely, we would give some semi-quantitative thing.

DR. FELIX: I do semi-quantitation on certain -- not on others.

DR. DAVEY: Proliferation, I guess would be -- sometimes ERPR.

DR. O'LEARY: Okay. Thank you.

You have had -- yes, Ms. Rosenthal.

MS. ROSENTHAL: I don't know who to address this question to, but I am looking at the graph of the time to progression at 2+ patients and 3+ patients. Who would I address the question to?

DR. O'LEARY: That would be Dr. Jerian.

MS. ROSENTHAL: And for some reason if you superimpose one graph on the other, the 2+ patients very rapidly goes downhill and seem to demonstrate no advantage. Then the 3+ has a definite advantage. Is there a possibility that the use of Herceptin on a patient who is not -- who has not advanced enough to be called the 3+ is actually counterproductive because is this not a progressive disease that goes from 2+ to 3+? No? It is an absolute?

DR. JERIAN: I don't think we can say that. We

don't have all the survival data. So, I don't know if any of the toxicities play into that at all, but we can't make any conclusions about that.

DR. KEMENY: But the concept of the progressing is not something we know about. Generally, people either have it or they don't have it. We don't really know about progressing.

MS. ROSENTHAL: So, we don't know if you are 2+ that you go to 3+. They just -- that is what I mean.

DR. JERIAN: You also don't know if a biopsy from one site from a biopsy at another site. We don't know -- you know, a patient's lymph node here could be 2+; whereas, their liver could be 3+. We don't know. We don't know that information.

DR. HORTIN: I had one other question about the clinical data and that was in the evaluation of the progression of disease, was there any examination of the percent of positive cells as a factor in terms of progressions? Because actually there seemed to be a fairly wide distribution of percentages. If you look at the raw data, it looks like a fairly wide distribution from, say, the three positive staining cells range from as few as 20 percent through up to greater than 90 percent positive.

I was wondering if there was any examination of whether there was correlation with survival or response to

the Herceptin with that.

DR. JERIAN: The only data that I received from the sponsor on 2+ and 3+ is whether it was 2+ or 3+. I don't have percentages of cell staining 2+ or 3+.

DR. HORTIN: An issue for the doctor representatives would be how they arrived at the cutoff point of 10 percent as acceptable or a cutoff in terms of being a significant number. I didn't see that we were presented any data to indicate whether 10 percent would be a representative number in terms of assessing the positivity of staining.

DR. COHEN: I think the answer to that question is better addressed to us. That was the cutoff used from the beginning of our clinical development in 1992. I am not sure that the basis for it is known to us at this time. But we could certainly undertake to understand it.

DR. HORTIN: One of the bases for my question here is I was wondering whether in terms of the reporting -- we have been grappling with the issue of how to grade them or how to report them, but is it going to be important at some point to know percentage? Are people going to need to report that in terms of either internal quality indicator or is it going to be some sort of prognostic indicator that is going to be useful down the road that people are going to need the data for?

Maybe you could address that.

DR. COHEN: I think, as Dr. Jerian said, we are unaware of any prognostic implications of it. I think in terms of the way the laboratory studies have been conducted in the past -- I suppose Steve could comment if you are interested. But there are certainly examples of 3+ overexpression, real 3+ overexpression with a high level of membrane intensity that are seen in 10 or 15 or 20 or 25 percent of the cells.

While the prognostic implications may not be clear, certainly the 2+, 3+ data that you have looked at is what we have. I think the intensity of that membrane staining suggests that it is real and we have no additional information on that.

We have always used 10 percent as our cutoff. If 10 percent of the cells do not stain, it is not a positive stain.

DR. O'LEARY: Dr. Ladoulis, you look like you had -- no?

DR. LADOULIS: I am rethinking the issue all over again for probably the fifth time today. This whole issue about scoring of immunohistochemistry everybody knows is a real problem and there are articles on different ways of doing scoring having to do with both the intensity and the numbers of the cells. This is not a consensus.

What we have to deal with is what we have and maybe the best thing that we could do -- and I raise this to members of the committee for some kind of resolution here and let's come to closure.

We have data based on the scoring scheme as you have defined it in the -- as long as it is well-defined in the insert labeling, as to how the laboratory staff is to do the scoring and as long as it is specified that really the 3+ score is the only one for which valid outcome data seems to be consistent, that is, I think, all we can do at this point in terms of making a recommendation.

We certainly, I think, have agreed on the concordance with these previous results and the fact that it is predictable, at least at a certain level, the 3+. And, you know, what clinicians will choose to do is not what we are seeking to force or to predict, just as with other tumor markers. But we want to make sure that the claims are verifiable and substantiated by the data.

If it is a semantic problem, we can probably leave it as it was proposed in terms of the current scoring. If we want to make labeling changes in order to make sure that they are not misunderstood, there are no semantic arguments about it, we can change the labeling and the agency can work through that.

DR. O'LEARY: I am going to go ahead and just run

around the table to address this issue as it is written and if you, you know, want a clear threshold, please say that that is what you would prefer and if you prefer to suggest that the score be reported raw, please, say that.

DR. DAVEY: Do you want him to say anything --

DR. O'LEARY: No, I think he has already addressed that. If he wants to say more, he is welcome.

DR. LADOULIS: My only qualification would be that the scoring of 3+ is the only one for which data have been presented to show a clear clinical benefit in the Herceptin study.

DR. O'LEARY: Would you recommend that that would be something that would be put in the report?

Yes, Dr. Maxim.

DR. MAXIM: As I think I began this morning, I said this was going to be a difficult issue and you certainly proved me correct. I have to thank you for that.

Again, I think what we are looking at here are two different studies, as Dr. Miller brought out, which used the LabCorp assay to select patients and you had clinical outcome from that. Here you are looking at concordance of the DAKO assay with the LabCorp.

I was at the ODAC meeting two days ago -- and Dr. Miller can correct me if I am wrong, but I believe that at least one of the recommendations that came out of that was

that although the most pronounced clinical benefit for Herceptin therapy was with the 3+ patients.

There was enough clinical benefit to use the drug in 2+ patients, that they should not be excluded from being candidates for therapy.

DR. FELIX: Is that from some data that we haven't been presented?

DR. MILLER: No, the study was designed to look at 2+ and 3+. The post-data is a subset review that wasn't written into the original trial and that is what the oncologist -- that is what the committee members have said, that they don't feel comfortable based on a small subset of populations, making those determinates when the study was not designed to do that.

The thing that you are voting on here is --

DR. O'LEARY: We are not voting.

DR. MILLER: -- discussing here is the packaging label for the test. We shouldn't say anything about clinical utilization of a drug in the packaging label for a test. You are going to say that this equals this and this equals this as a clinical test.

DR. O'LEARY: Well, it goes together with the label for use.

[Multiple discussions.]

DR. DAVEY: We get questions from clinicians all

the time. I disagree completely.

DR. MILLER: -- what it means, but I mean you are not going to say in the labeling for the test that if it is 3+, that that patient goes -- you are not going to say that if it is 3+ that means the patient highly overexpresses HER2.

DR. FELIX: We haven't demonstrated that at all.

DR. JERIAN: Can I just make a couple of points that might clarify some of the clinical data?

First, in the Phase 2 where Herceptin was administered alone, there were two patients who had tumor responses and they were real tumor responses, who were 2+ patients. That is a slightly different question than the idea of adding Herceptin to chemotherapy, where we don't really see -- it is a little harder to sort out specifically the effect because you are using it in combination with agents that are already very active in the disease.

But there when we analyze the data it is much less impressive, as you can see. So, there are two different scenarios where a clinician would apply it.

The other thing I might throw out, we don't have to use the term "indeterminate." One thing that Dr. Segal had suggested was the idea of strongly positive and weakly positive in providing the data in the package insert.

So, I just wanted to throw out those two ideas for

you to consider.

DR. FELIX: Yes. And your suggestion that these are two different and independent concepts are -- as an independent product, there is certainly not enough data here to substantiate anything. This is completely linked, completely linked to the data that was done on the Herceptin trial. I mean, if you dissociate those two, we don't have enough data here to say that there is antibody expression at all. I mean, there are 40 cases.

So, I think that -- I guess we should continue going around the table.

DR. O'LEARY: Let's go ahead.

DR. DAVEY: I was just going to say that, you know, again, it is not an exact correlation, but the clinicians, I would say, if you give them a 2+ result are going to think about the 2+ result in the clinical trials, even though they weren't exactly the same assay. So, I do think that we need to say something.

I would strongly vote for the weak -- and I was going to bring that up, too -- the weak and the strong positive and put that in the labeling as a recommendation for laboratories to differentiate between the 2+ and the 3+ by weak and strong positive.

Then I would also say that there should be some information given carefully saying that the 3+, although

there was not a perfect correlation between 3+ in this assay and 3+ in the clinical trial assay, that there was more information. I wouldn't say that there was no information but there is more information known for the 3+. That is the way I would say that.

DR. O'LEARY: Remember that our discussions really are in large part here to sort of inform the FDA staff, too, of the heterogeneity of you and perhaps confuse them even more.

Dr. Hortin.

DR. HORTIN: I would favor basically somewhere in the package insert saying that 0 and 1+ results are essentially negative for amplification and a 2+ is a weak positive and a 3+ is a strong positive, something to that effect -- and how these correlate to the HER2 application. And I think actually the population that may benefit from that most may not be so much the oncologists but it may be actually be the patients or people who will hear about some result coming back. And for the 1+ positive, they will say, well say, well, it is weakly positive. It will either hold out some hope that they will have response to the therapy or they will basically hunt around from one oncologist to another until they will find somebody to give Herceptin because there is this small hope held out to them that they may be one of the people who may be responsive.

And, of course, at this point, we have no data to that. I think that that information -- it is important to convey that in our current understanding that those people are negative for a substantial amplification.

DR. O'LEARY: Dr. Felix.

DR. FELIX: I believe that it is important to substratify it and give it a numerical value, 0, 1, 2 or 3. And I think that I am coming rapidly to the conclusion that if some level of positivity has to be assigned, which I think it is our responsibility to assign it, that 3 be called strongly positive and 2 weakly positive. The other two called negative also.

DR. O'LEARY: Dr. Miller.

DR. MILLER: I think they should be a numerical grade and I think that is a very reasonable assumption of strongly or weakly positive for a 2+ and 3+.

DR. O'LEARY: Thank you.

Dr. Floyd.

DR. FLOYD: I agree that we should keep the grading and the verbiage that we recommend is something that will be pasted into the pathologist department's word processors. We can recommend that. Whether it gets put in in all cases is another issue.

DR. O'LEARY: Ms. Rosenthal.

I think in a perfect world where 3+ were 3+ were

3+ it would be a different -- we would have a different story, but given the results of the difference between the CTA and DAKO staining, where we have perfect agreement, 52 percent concordance and agreement to a plus or minus one level 89 percent, I think we have to allow the 2+ patient to explore the benefit of Herceptin.

So, I would vote for what is it, a weak positive and a strong positive, so, with the numerical evaluation.

DR. O'LEARY: Dr. Kemeny.

DR. KEMENY: I would agree that we should keep the numerical terminology and if you want to put on the modifiers of "strongly" and "weakly," I don't see any problem with that. But I do think -- and as we just heard from Dr. Swain, from a clinical point of view for the patients, it is very important that we don't use words like "indeterminate" and that we have numbers that go along with the findings.

DR. O'LEARY: I think that that consensus is pretty clear at this point. So, we can move on to the fourth question, which is that there are technical difficulties commonly associated with immunohistochemical assays that were also evident during the inter-laboratory reproducibility study.

Should DAKO sponsor a training program to educate and train users how to perform the test, including the

proper use of the control slide to validate the assay and aid in interpretation of results? Are there additional issues that training should include?

So, I guess, you know, there are two questions there and everybody should feel free to address either or both.

Dr. Kemeny.

DR. KEMENY: Now, not being a pathologist, is this usual? Do you usually have a training program to educate people on how to use a --

DR. O'LEARY: It depends. We see it, for instance, in PAP smear stainers or not stainers, but the rescreen or prescreening devices.

DR. LADOULIS: But I think this is not usual in the sense that the professional societies actually do a great deal of this. They need histochemistry specialties, the pathologists, immunopathology groups. I am not sure that it would be necessary nor contribute anything to actually have this as a recommendation to the sponsor to conduct this; whereas, in the immunohistochemistry societies and pathology societies, already there is a lot of activity going on trying to achieve consensus at all times about immunohistochemistry staining. It is very difficult.

I think it would only complicate and that is introducing another body trying to carry out some training

program and maybe conflict with ongoing efforts in the specialty societies.

DR. DAVEY: I guess I have to disagree. I think that we should push the company to provide as much educational help. Now, I don't know whether it should be an on-site course that people go to. I think that they need to provide availability of experts that you could send slides to for interpretation, either send the slides if the laboratory was having problems figuring out what was 2+, what was 1+, so that they could send them to someone at the company.

I do think professional societies need to work on it and I think they need to, you know, try to work maybe or provide at least guidance to -- like if a CAP wants to develop a proficiency testing program, that there should be encouragement to help provide how things should be processed, you know, getting the things out so that they can be sent out and processed within a timely fashion, so the slides don't deteriorate.

So, I think we should encourage the company to do a lot because I have seen some problems with some of the cytology things where some companies did not maybe provide -- we see, for example, Cytek(?) in the adequacy business where they have sort of copped out with that. I think we should approach them to give us more information at the time

of approval.

So, I think we need to get more pictures. I think we need to send out lots of pictures the first time, more than just one or two examples -- lots of pictures, maybe sponsor workshops but also provide to professional societies pictures to use at workshops; I think, also being available for development of proficiency testing would be helpful.

DR. O'LEARY: Dr. Hortin.

DR. HORTIN: I think the biggest deficiency I see in terms of information or training is really kind of the vagueness of their procedures and their direction, that there needs to be carried out much more specifically standards for how to do your tissue fixation, what acceptable time periods of sample stipivity(?) are and basically how to do the heating procedure. All these should be spelled out in great detail and should basically be standardized.

I mean, there shouldn't be -- based on the limited information we have here, we have no way, if somebody sticks in a pressure cooker or somebody else sticks it in a microwave, whether the results are going to be in any way equivalent. I think from the standpoint of training materials or standardization, really, the procedure needs to be spelled out much more specifically and in greater detail than what is here.

I see that is perhaps -- additional training materials kind of get people up to speed and to look at their proficiency testing issues and others. I think that is kind of a general need in the area. I don't know to kind of focus on this specific test -- I don't know that is necessarily bad. I think that may be a problem of the whole field to some degree and needs to be addressed from the entire field of immunohistochemistry.

But I think that there are simple things in terms of spelling out exactly how the procedure should be done may help considerably in terms of assuring that people are going to get some quality results and that they don't kind of make their own homemade adaptations for their own site that may not work equivalently. That is my greater concern, rather than having kind of a detailed training program going in and teaching people from the start.

DR. O'LEARY: Thank you.

Dr. Felix.

DR. FELIX: I always think education is useful and the question that I always sort of struggle with is how much and how do you confirm the efficacy. You can lead a horse but you can't make them drink and there is always going to be some laboratories that will go through a training and really do very well with it.

I think that there certainly should be a minimum

of a customer service branch or some sort of service that the company provide all laboratories that will help them get this test running. I don't know if bringing people to a central location and teaching them how to boil slides for 20 minutes is really going to do much, but I think that there should be certainly a minimum customer service that they should provide now. I think that is perfectly reasonable. I would probably stop there.

DR. O'LEARY: Dr. Miller.

DR. MILLER: I would like to pass just to people who have more to do with this.

DR. O'LEARY: Dr. Floyd.

DR. FLOYD: I have been involved in the support of immunohistochemistry product lines in point of fact for a client several years ago, taking every customer call that comes in. I can tell you that the last thing the customer does is read the product insert. They call customer support first.

I can also tell you that immunostaining in the U.S. started with the continuing education efforts of DAKO Corporation. They gave all the original workshops all over the country, introduced most histology labs to this and set up a standard about which every other company is judged.

I can also tell you that it has been mentioned, the pathology associations have continuing education

courses. Week after next in Salt Lake City, the histotechnologists, the technicians, who actually do this, will be meeting. There are four days of continuing education workshops. There are almost 180 workshops being presented over 40 percent of which are devoted specifically to immunostaining and the ways in which to standardize and do it.

So, these efforts are going on. Those efforts have been supported by DAKO and the other suppliers to this industry. So, this is a continuing education effort that is continuing both by the pathologists and by the practitioners in the laboratory. I think this is something that we can make a lot of suggestions for what we want to have included in the product insert and I think that is valid. But there comes a time when the company has no more control over the way a product is used once a customer buys it.

I think that this particular question is something that is probably not really appropriate. It is certainly appropriate for us to talk about what goes in the product insert. I don't know if you can actually say we have a way to force users to use something a certain way.

DR. O'LEARY: Thank you, Dr. Floyd.

Ms. Rosenthal.

MS. ROSENTHAL: So sorry Dr. Floyd said that because I was just going to say I feel very strongly that

there should be additional training to people who are going to use this given the information we have seen and the few problems, not so few, that we have seen under optimal circumstances and considering the aging eye, looking at the variably prepared slides with varying levels of caffeine in their blood, you know. And let's not forget the patient at the other end, who is clinging to their life and really needs to be as perfect as it can be. I just feel that the training for this should be included.

DR. O'LEARY: Dr. Kemeny.

DR. KEMENY: I will pass on this one.

DR. DAVEY: Can I make one more comment?

DR. O'LEARY: Sure, Dr. Davey.

DR. DAVEY: I do think this is a little bit different than the standard immunohistochemistry kit and I think that, you know, we are really, you know, making a decision using a drug and most of the other immunohistochemical kits, maybe ERPR is another exception, it is used in context with a lot of other information. So, I am not sure that this is exactly -- and that is why, I guess, I feel a little bit more strongly than we have a little bit more particularly pictures, I think, is the thing I felt most strongly about, more Kodachrome, something available to the user to judge this.

DR. O'LEARY: A comment from Dr. Lebinowitz(?).

DR. LEBINOWITZ: I just wanted to make a comment.

For the immunohistochemistry tests in general, it is a "yes" or "no." The only other IHC product that FDA has approved that is semi-quantitative is the Abbott estrogen receptor and part of the approval was that the manufacturer supply a calibrator slide as it were, that was traceable to a biochemical test, so that the tumor that is used to make the calibrator slide was actually tested against the biochemical level. So, it was very important here with this semi-quantitative aspect, to have something traceable.

That is why the manufacturer on their own has provided the 1+ and 3+ slide to calibrate. So, that made this test something that we could feel would be a reliable semi-quantitation as opposed to the usual positive control and negative control.

DR. O'LEARY: Thank you.

Since we are not taking a vote, I don't normally vote, but I do get the opportunity to comment, I think that from my perspective, I am not as certain about the need for a specific training course one way or the other. However, I think that this test, as with other immunohistochemical tests, it is going to be a potential problem in the absence of efficiency testing material.

I think that proficiency testing in every single area of the laboratory has perhaps been the single most

important driver for consistency in laboratory testing in the United States.

I would think it would be incumbent upon the professional community, the community of manufacturers and the government community together to make sure that if this type of product is out on the market, that we have proficiency testing that allows us to make sure that we can get at least consistent results from place to place and day to day because failing that, then questions like postmarket surveillance to answer the question, 2+ versus 3+, become much more difficult to answer in a meaningful way that can be interpreted by anybody.

So, I think we have some heterogeneity on this issue with a majority thinking perhaps not, but that the manufacturer should certainly make it possible to get education anyway.

Is that a fair assumption about the synopsis committee view? Split but we ought to be able to be educated.

Dr. Ladoulis.

DR. LADOULIS: There certainly is a precedent for other manufacturers, for other types of laboratories to provide on-site training for the laboratory staff. Certainly, flow cytometry comes to mind exactly. So, there may be some way in which the agency could stipulate that the

personnel performing these tests need to be qualified personnel, however you want to specify that qualification by virtue of either manufacturers or training or whatever.

DR. GUTMAN: There are two different routes. It is not a common practice. There have been other products which have been either been approved or cleared that have training, even in some cases sort of -- some requirement that there be some training program be the usual. So, this isn't necessarily precedent setting. I think it depends on how far you go in terms of what training requirements you impose.

The agency also can, without a great deal of force, can require certain levels of expertise. We can't require someone to be certified in a particular discipline or have an absolutely specific type of educational threshold, but we can require certain kinds of training or experience requirements for use of a product.

It is not clear to me from having listened to this discussion that you have necessarily -- you certainly haven't harmed us in terms of giving us narrow bounds. I don't know how much help there is in terms of what kind of negotiation we would have with the company to determine an appropriate training setting. If folks have thoughts about this after the panel meeting, you are welcome to give us input because this, obviously, is of enough interest to both

you and us that we are going to want to talk to the company about what the right balance and thresholds are.

DR. LADOULIS: I just wanted to give one other reassurance for the consumer representative and patients and physicians. This particular assay is going to be done on biopsy material. It is going to be done in a hospital laboratory or a reference pathology laboratory setting. It is not like cells that might lend themselves to be done in an office setting in which a physician office laboratory would be in a position to perform them.

So, the likelihood that this test will be performed in a certified laboratory with qualified personnel is very high. I think I am pretty confident that because of the requirements of the material that is required from the biopsy, the likelihood that there are unqualified people and unqualified laboratories performing this is very unlikely.

And even if it is because of the very nature of the surgeons and the oncologists, they will be assured that they are going to submit these tissues only to those people who do them. I feel confident. This is not a major issue.

DR. O'LEARY: Can I actually ask a question and comment? The question is is the sale of this anticipated to be restricted to certified clinical laboratories?

DR. GUTMAN: I don't think they have a choice. My understanding is in this country, at least -- I don't know

about abroad, but in this country that is not an option that -- that you can't perform tests outside of that setting. This test is clearly a high complexity test.

DR. O'LEARY: I was just wanting to make sure.

DR. DAVEY: I think to report it out. I mean, maybe you can order it and use it in a research setting, but I think to report out --

DR. O'LEARY: I know what the law is at the end of the -- the physician, yes.

DR. DAVEY: In reporting it out, it has -- you are right. It is high complexity. So, they have to be precertified.

DR. O'LEARY: That is certainly true for reporting out immunohistochemistry. Obviously, immunohistochemical tests are used for other purposes and what I am, you know, just asking about is the end around potential.

I think the last question is: Do members of the panel see any additional issues or differences between the DAKO test and the LabCorp test that should be considered? I suppose if so, what are they?

Dr. Ladoulis.

DR. LADOULIS: No, I don't have any other comment.

DR. DAVEY: I just have one question. This has to do with the Herceptin use. If both of these are approved, will the -- is there any restrictions on having to use an

FDA-approved test to determine whether a patient goes on Herceptin therapy or is it pretty much just that you would hope that that would happen?

DR. JERIAN: The labeling for Herceptin would indicate you would need to use this test for protein overexpression. There is another test that is approved that detects DNA amplification. That has not been tested in this clinical study.

DR. DAVEY: Okay. So, the labeling would say that you would need to use this test.

DR. JERIAN: This specific test, yes.

DR. O'LEARY: Dr. Hortin.

DR. HORTIN: I think I already raised my concerns in terms of -- they don't specifically relate so much to the direct comparison as the DAKO and the LabCorp test. They relate mainly to issues in terms of standardizing the test.

I thought the one area -- it does relate somewhat in terms of the comparison was there may be some question about the validity of the data to some degree, in terms -- without knowing how stable the antigen is, you do not know -- and we don't have figures for how old all these samples are. It may be that some of the grading would have changed for some of the specimens, depending on how recently the samples have been collected.

I think that that is actually a fairly critical

issue that could probably be addressed fairly simply. We are not talking about six months stability or a year stability. I mean, we are talking primarily about how stable are the samples over a two week time period or maybe up to four weeks or so, there is evidence that certainly the six month stability is unfavorable and that those with the undesirable samples to go back in your archives and pull out a block out of your sample for maybe somebody who had their breast tissue taken out six months ago or two years ago and now they have decided, well, I would like to know what my HER2 status is and whether I would be eligible for this trial.

But I see that as the issues of the standardization and I would hope that there would be some data for it come in terms of the -- that would better address the sample stability issue.

DR. O'LEARY: Dr. Hortin, would you suggest -- and other members, would you suggest that in the same way that a drug package insert might say that safety and effectiveness in pregnancy hasn't been established, but specific pertinent negatives, that, you know, effectiveness of this assay on tissues older than x, you know, weeks or months have not been established, things of that sort be put specifically in the insert?

DR. HORTIN: Well, I think the problem is we don't

know what that threshold is. I mean, we know that six months is bad. We don't know if one month or two months is. I guess based on -- you could maybe get some feel for that, I guess, based on how fresh the samples were some of these studies. They seemed to work -- most of these samples were probably a week or two old. They probably worked all right for those samples. So, we have a sense that you can get some reasonable data, but maybe some of the reasons why sometimes the results don't look quite as clean as they should is the kind of compounding issue about sample age that actually might be -- it might actually be making the data look worse than it actually is if you extremely fresh samples.

DR. DAVEY: The blocks versus the slides, I think we are getting confused. I think we need to make clear it seems like a lot of the blocks are quite old, with the slide issue. So, I am glad you brought that up, though, but I -- maybe we should suggest some sort of postmarketing studies or by studies by the company because it would be pretty easy to cut a block of breast tissue and then test it at different time intervals under different conditions and then that would provide more data to the laboratories because sometimes there is a tendency to cut a whole bunch of slides at once on a block.

And then do the stains at different times,

depending on when you have a run. So, it would be -- because you don't -- the kit is going to be, obviously, somewhat -- you don't want to just do one patient sample at a time. I think we have to -- it would be useful to have more information on that.

DR. O'LEARY: Okay. Thank you.

Dr. Felix.

DR. FELIX: I agree with that. I don't that testing the blockage would do any good. I think that is fairly well-established. I think that what they are referring to is testing the slides. I think it is a relatively easy thing to do and it probably would be very helpful for laboratories to have at least a reasonable period tested, probably four to six weeks, which would be very easy for the company to provide that data, I think.

I think it would be helpful. I agree with Dr. Hortin regarding very specific statements in the package insert regarding antigen retrieval. I think that they should strongly recommend the procedure that they use that is optimal.

DR. O'LEARY: Dr. Miller.

DR. MILLER: I have no further comments.

DR. O'LEARY: Dr. Floyd.

DR. FLOYD: I didn't see any differences between them.

DR. O'LEARY: Ms. Rosenthal.

MS. ROSENTHAL: None.

DR. O'LEARY: Dr. Kemeny.

DR. KEMENY: None.

DR. O'LEARY: I guess my only additional comment in would be in the area of postmarket surveillance. I am still troubled by the fact that this is a test for a test, that we are using this test more or less to predict the result of a test, which was used to select for clinical outcome and, hence, it would be nice to eventually, in combination with Genentech, have the data that linked this test result directly to clinical outcomes.

And I would urge CBER and CDRH to come together to facilitate in whatever ways possible the acquisition of this data and based upon that data to revise as necessary or not the way this thing is labeled and marketed.

That takes us, I think, through the five issues that were put forth to us. Dr. Gutman, has this --

DR. GUTMAN: Fine, very helpful.

DR. O'LEARY: Is there anything else that has come to your mind or to Nina Chace's mind, Max, Peter, anyone that you would like to put forth or new concerns?

I know you are always way ahead of us.

DR. GUTMAN: I think we pass.

DR. O'LEARY: Thank you.

In that case, this portion of the meeting beginning at 2:00 p.m., is, again, open for an open public hearing. And the meaning in this case is that if there is anybody here that would like to address the committee as a whole prior coming down to vote on approvability and conditions regarding what has gone on so far or other issues, they are invited to please come forward, identify themselves and their affiliation and comment.

Is there anybody who would like to present?

[There was no response.]

Okay. If not, that brings us really to -- I will then close the open public hearing and we have a choice and I will leave it up to the panel members whether we take a break at this point, as would be called for, or we go right on doing the vote and recommendations.

DR. DAVEY: Is it appropriate now to ask if the company has any comments?

DR. O'LEARY: That was more or less what -- they were certainly welcome to come forward and they are still welcome to come forward if they want to make any comment.

DR. DAVEY: I wasn't sure if that included the company or not.

DR. O'LEARY: Yes, that includes any interested person.

Okay. In that case, we really don't need a break

right now and I know that Dr. Miller needs to leave. So, we are going to have a clarification now from Veronica Calvin, our executive secretary, regarding voting procedures and how the rest of this meeting will go.

Agenda Item: Panel Vote and Recommendations to FDA

MS. CALVIN: Dr. O'Leary will now be calling for a motion and he will be asking the temporary voting member to vote for whether this PMA should be approved, approved with conditions or not approved.

To reiterate, the voting members present are Dr. Diane Davey, Dr. Juan Felix, Dr. Charles Ladoulis, Dr. Glen Hortin and Dr. Mary Kemeny. Appointed as a temporary voting member for today is Dr. Carole Miller.

The panel vote may take one of three forms: one, approval with no attached conditions; two, approvable with conditions, for example, resolution of clearly identified deficiencies, which have been cited by you or the FDA staff. These may include data clarifications or changes you would like to see in the draft labeling.

Three, not approvable. Section 515(d)(2) Paragraphs (a) through (e) of the FD&C Act state that a PMA can be denied approval for any of five reasons, three of which are applicable to panel deliberations. The three reasons for recommending not approvable are: There is a

lack of showing of reasonable assurance that such device is safe under the conditions of use prescribed, recommended or suggested in the proposed labeling thereof. There is a lack of showing of reasonable assurance that the device is effective under the conditions of use prescribed, recommended or suggested in the proposed labeling thereof.

And the third reason is based on a fair evaluation of all material facts, the proposed labeling is false or misleading in any particular. To clarify the definition of "safe," there is a reasonable assurance that a device is safe when it can be determined based upon valid scientific evidence that the probable benefits to health from use of the device for its intended uses and conditions of use when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risk.

To clarify the definition of "effective," there is a reasonable assurance that a device is effective when it can be determined based upon valid scientific evidence that in a significant portion of the target population, the use of the device for its intended uses and conditions of use when accompanied by adequate directions for use and warnings against unsafe use will provide a clinically significant result.

If you vote not approvable, we ask that you identify the measures that you believe are necessary to

place the PMA in an approvable form.

Thank you.

DR. O'LEARY: Thank you.

So, at this time, we are open for a motion.

DR. DAVEY: I will do one if no one -- okay. I am going to recommend approval with conditions and the conditions would be to have additional labeling information on the weak, something like the strength of the --

DR. O'LEARY: Stop. Can I ask you to --

DR. DAVEY: We don't need to do that?

DR. O'LEARY: No, no, that is fine.

I am going to ask a favor. Dr. Ladoulis, would you be willing to keep sort of track of these conditions for us so that as the discussion goes on, we can -- thank you very, very much.

DR. DAVEY: Okay. I don't know how detailed I want to get, but something specifying the strength of the results and giving additional information on the label about maybe weak or strong or something else that the FDA and the company agrees on.

Also, the importance of the things like the water bath, making more information available on the label. So, I think part of it is labeling and also more pictures available to the user on 1+, 2+ and the strength.

Then, finally, some postmarketing or some kind of

studies on the stability of the slides so that the company provide more information to the user on the stability. So, I guess, more labeling information, which I think they have already conceded they needed to do and more information to use around the strength of the result.

DR. O'LEARY: Prior to calling for a second, I would like to ask if there are any suggested modifications or clarifications.

DR. FELIX: I think we have all sort of been nodding about the postmarket approval accrual of clinical data. I would like to propose that that is added to the list of things that we recommend.

DR. O'LEARY: Dr. Davey, is that --

DR. DAVEY: That is fine.

DR. O'LEARY: So, that has been added to the motion for approval that postmarket surveillance to validate this against patients clinically receiving the drug conducted. Do I understand correctly that -- are there other suggestions -- yes?

DR. HORTIN: I had a couple of specific items. I think the procedure very specifically spells out kind of acceptable fixatives and ones that may not be acceptable. The issue of the specimen age has already been identified. After the postmarketing studies have been done, it should spell out what an acceptable sample age would be.

The processing procedure in terms of antigen recovery should be spelled out and Dr. Davey also pointed out the interpretation should be spelled out. So, I think all those need to be laid out very clearly in the procedure and identified very clearly as the recommended procedure and there should be warnings against deviating from that, that it may affect the results obtained.

DR. O'LEARY: Okay. Dr. Davey, since this is a suggestion to your motion --

DR. DAVEY: No, I think that those clarify some of what I said.

DR. O'LEARY: Okay.

Can you summarize here, Dr. Ladoulis?

DR. LADOULIS: I will summarize the points that have been made so far. The recommendation, I guess, is for -- and I would second the motion. It is for approval with conditions, number one, that the scoring method be maintained with qualifications of strong intermediate or low amplification as indicated; No. 2, that the labeling provide specific instructions for the procedural conditions to be followed for the fixatives that are permitted to be used to give acceptable results and for cautions on the aging of tissue samples to be used.

That postmarketing surveillance or postmarketing accrual of clinical data be carried out and, finally,

labeling modifications to include cautions about scoring and interpretation and warning that there is no deviation from those procedures because it would affect the results.

DR. O'LEARY: Thank you.

DR. DAVEY: -- pictures provided, more visual aids provided.

DR. O'LEARY: And also, I think, that last segment on -- Dr. Felix, I think you are going to get this.

DR. FELIX: Yes. You introduced new language. I want to make sure that we all agree that that was new language. In the first thing that you said you said strong, intermediate and low. It should say no -- negative or no amplification, weak, positive --

DR. LADOULIS: What suggestion do you want to make, strong, intermediate --

DR. FELIX: I mean, the language we had used before was just different than the one you used --

PARTICIPANT: That is up to the FDA somewhat.

DR. O'LEARY: Sure.

But the other segment was that Dr. Felix's modification had stated and I didn't quite hear it in your synopsis. Perhaps that was me, that was a very precise definition, not only of the interpretation phase, but actually of the entire procedure to include, you know, the time from, I guess, specimen acquisition and fixation,

antigen retrieval and so forth and a warning be given regarding the -- or a strong recommendation be given that they not deviate. Is that -- did I synopsize --

PARTICIPANT: That was Hortin.

DR. O'LEARY: That was Dr. Hortin. I am sorry.

Okay. Thank you. Are there other -- as I said, this is still under discussion and can be modified -- are there other suggestions?

Dr. Kemeny? No.

Dr. Floyd. Dr. Miller.

Okay. So, do all members of the panel believe they understand the motion first of all? Okay.

So, we have a motion. We have a second. So, we will now poll the panel again by name. We would like to state your vote on the motion and then to give a brief statement of the reason for voting the way you go as we go around.

So, I am going to run from my seat in alphabetical order. Dr. Davey.

DR. DAVEY: Okay. I vote for approval with conditions. And I believe that the company has shown a sufficient concordance with the clinical test and that is why I am voting for it, but I do think that there are -- the reason for the conditions is that there are just a few concerns about additional information that users would have

to have available.

Is that enough?

DR. O'LEARY: It sounds good to me.

Okay. Next, Dr. Felix.

DR. FELIX: Juan Felix. I also vote to approve with the stipulated conditions. I believe that this is a pretty remarkable set of conditions that we are being presented. This is the first time that I am aware of the approval of a diagnostic test that will permit patients to receive a therapy and almost exclude patients. So, I think that it is important for us to give approval to this in order to be able to treat these patients.

I think that the recommendations for continuing accrual of data is important because this is a very new test and it is associated with therapy. So, I think we need to know more about it.

DR. O'LEARY: Thank you.

Dr. Hortin.

DR. HORTIN: I vote to approve with conditions. I think that they demonstrated that in a very controlled setting the test can provide some useful data. I was actually somewhat appalled by kind of the current state of the package insert in terms of the lack of direction it gives and lack of standardization. I think that the data that they presented in terms of comparative studies showing

that approximately half the sites could perform the test adequately is not very reassuring and that we need to give a little bit more guidance in terms of standardizing and making sure that the procedure is performed accurately since it will have such a critical impact potentially in terms of the management of the patients.

DR. O'LEARY: Thank you.

Dr. Kemeny.

DR. KEMENY: I vote to approve with conditions. I feel that the company has shown that this will be a useful test and I think the conditions are reasonable.

DR. O'LEARY: Dr. Ladoulis.

DR. LADOULIS: I vote to approve with conditions that we have already stipulated because the test is definitely concordant with previous results and this will afford patients an opportunity to get a very valuable and useful treatment as it appears. And the cautions particularly I have in the conditions that we have stipulated, that the company assure the labeling instructions, that the performance of the test will be strictly adhered to and will comport the high standard so that we can assure the patients get enrolled.

DR. O'LEARY: Dr. Miller.

DR. MILLER: I agree with approval with the conditions. I think that the company has met the criteria

for approval and with these modifications we should be able to mark the labeling adequate.

DR. O'LEARY: Well, with that then the motion for approvability with conditions does carry.

That will bring us to close, I believe. Do we have some administrative closing announcements from you?

MS. CALVIN: No, just thank you to the panel, the sponsors and also the FDA staff. That includes CBER members. And thank you to the public attendees.

I want to acknowledge the other executive secretary for the Immunology Devices Panel, Louise Magruder and to thank her for all of her assistance as well.

DR. O'LEARY: I, in turn, would like also to thank, first of all, the members of the panel, who have given their time to be with us today, the members of the FDA staff who did an absolutely dynamite job, both on the CBER side and the CDRH side, in doing the reviews on this set of products -- I think it was phenomenal -- and those of you representing Genentech and your collaborators that brought this product forth for consideration.

Thank you.

MS. CALVIN: There is one other thing real quick.

For those of you who came in around 9:30 at the time the meeting was originally scheduled and you weren't aware of the change, that it was starting at 8:00, we have

handouts from everything that took place between 8:00 and 9:30 outside on the table if you are interested.

Thank you.

[Whereupon, at 2:18 p.m., the meeting was concluded.]